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Metal Complexes of Schiff Base Ligands.
Studies on the Formation of Macrocyclic Condensates

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Evidence is presented that the template formation of macrocyclic complexes of CR and related ligands (Fig. 1) (i) requires a minimum ring size, given in Figure 1 by $x = y = 3$; (ii) depends upon strong complexation of the metal at the pH of the reaction by the triamine reactant, such that the solubility product of the metal hydroxide is never exceeded; (iii) proceeds through a ternary intermediate complex.

Details are given of some new macrocyclic complexes prepared in the course of this study.

Introduction

Complexes of CR (Fig. 1) have been extensively investigated by Busch and others[1] and accounts of their properties have appeared in review.[2] Interest in compounds of this kind,[3] particularly as possible bioorganic models,[4] has led us to attempt to systematize the conditions for their preparation. Since no complexes other than those of CR itself have been reported, we first attempted to prepare complexes with different values of x and y, and different R groups.

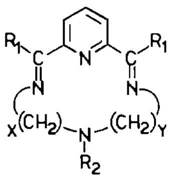

Figure 1. Derivatives of the ligand CR. Nomenclature is as follows:

abbreviation	x	y	R_1	R_2
CR	3	3	CH_3	H
N–Me–CR	3	3	CH_3	CH_3
des-diMe-CR	3	3	H	H
A,B–CR	A	B	CH_3	H

Experimental

CR complexes are readily prepared by template condensation. The metal salt, amine and diketone are refluxed together in equimolar ratio in a suitable solvent.

Method A[1]

2,6-diacetylpyridine (DAP) and 3,3′-diamino-di-n-propylamine – or their analogues* – are refluxed in 50% v/v aqueous ethanol with the metal salt for six hours. Typical concentrations are 0.2 mol l^{-1}. The disappearance of DAP may be followed by T.L.C. ($CHCl_3$ on silica); since neither the other reactants nor the ionic products are eluted by chloroform the appearance of side-products may also be followed. After refluxing the ethanol is removed by evaporation.

Method B[5]

The refluxing is carried out at 105° C in 50% v/v aqueous dimethylformamide using 0.5 mol l^{-1} concentrations of reactants. The higher temperature brings about complete condensation in 10–20 minutes, but produces more side-products, in particular a red–brown self-condensate of DAP.

In either method the product, in typically 50% yield, is precipitated by the addition of concentrated aqueous sodium perchlorate, and recrystallised from water. The complexes of 3,4-CR, however, gave a poor yield on recrystallisation from water, suggesting partial decomposition. They were purified by dissolving in acetonitrile and reprecipitating by the addition of diethyl ether. Analysis figures are presented in Table I. The use of ethanolic lithium halide solutions, previously employed[6] to bring down a bis-halide, was unsuccessful for copper and nickel CR complexes.

Syntheses

Compounds prepared as above are shown in Table I. Some of these require further comment.

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* DFP obtained from Raschig, the 3,2- and 3,4-triamines from Aldrich, and the N-Me triamine from Pfaltz and Bauer.

TABLE I. Microanalytical Data.[a]

Compound	Required %				Found %			
	C	H	N	Ionic Hal	C	H	N	Ionic Hal
$Ni\cdot3,4\text{-}CR\cdot2H_2O\cdot2ClO_4$	33.9	4.99	9.90		34.3	4.89	9.65	
$Ni\cdot3,4\text{-}CR\cdot H_2O\cdot2ClO_4$	35.0	4.78	10.2		35.1	4.70	10.2	
$Ni\cdot3,4\text{-}CR\cdot2ClO_4$	36.2	4.52	10.5		36.0	4.42	10.7	
$Cu\cdot3,4\text{-}CR\cdot H_2O\cdot2ClO_4$	34.8	4.74	10.0		35.0	4.74	10.0	
$Zn\cdot3,4\text{-}CR\cdot Br\cdot ClO_4$	37.2	4.69	10.8	15.1	37.0	4.56	10.9	15.5
$Cu\cdot DAP\cdot3,2\text{triamine}\cdot2ClO_4$	31.0	4.46	10.4		31.3	4.39	10.6	
$Zn\cdot N\text{-}MeCR\cdot Br\cdot ClO_4$	37.2	4.69	10.8		37.4	4.81	10.9	
$Cu\cdot N\text{-}MeCR\cdot Cl\cdot ClO_4\cdot H_2O$	39.8	5.32	11.4	11.6	39.4	5.18	11.6	11.4
$Zn\cdot$*des*-diMeCR$\cdot Br\cdot ClO_4$	32.9	3.82	11.8	16.9	32.8	3.89	11.7	16.8
$(Zn\cdot CR)_2\cdot OH\cdot H_2O\cdot3ClO_4$	36.8	4.84	11.4		36.8	4.59	11.4	
$Zn\cdot CR\cdot Br\cdot ClO_4$	35.8	4.36	11.1	16.1	35.6	4.55	11.7	16.2
$Zn\cdot CR\cdot2Br$	37.2	4.55	11.6	32.6	37.2	4.52	11.8	33.1
$Ni\cdot CR\cdot Cl\cdot ClO_4$	38.3	5.14	11.9	11.7	37.9	4.80	11.7	11.9

[a] All analyses were performed by Mr. D. Flory at these laboratories.

$Ni\cdot3,4\text{-}CR(H_2O)_n\cdot(ClO_4)_2$ crystallised from water as the pale brown dihydrate, which changed after several hours *in vacuo* to the orange monohydrate. Heating to 110° for 24 hours *in vacuo* gave a brick-red product, which analysed as the anhydrous complex (contrast the behaviour of the 3,3-CR homologue[1]). The marked colour changes indicate that the water was coordinated to the nickel.

$Cu\cdot DAP\cdot(3,2\text{-triamine})(ClO_4)_2$ was isolated as deep blue crystals at room temperature from the unheated reaction mixture of method A, and does not react further on prolonged refluxing. If the 3,3-triamine is used then the only product is $Cu\cdot CR^{2+}$, even at room temperature.

$Zn\cdot N\text{-}MeCR\cdot Br\cdot ClO_4$ was prepared by method A. However the preparation was successful only in the presence of a large excess of sodium bromide (see Discussion).

$Zn\cdot des\text{-}diMeCR\cdot Br\cdot ClO_4$ was prepared by replacing DAP with DFP (2,6-diformylpyridine) in method A; the reaction with DFP is much more rapid.

$Zn\cdot CR\cdot Br_2$ was prepared by the double decomposition in acetone of $Zn\cdot CR\cdot Br\cdot ClO_4$ and LiBr. The yield was quantitative – *cf* Ref. 6.

$(Zn\cdot CR)_2OH\cdot H_2O(ClO_4)_3$ was precipitated by adding concentrated sodium perchlorate to an aqueous solution of $Zn\cdot CR\cdot Br_2$ whose pH had been raised by addition of NaOH to a value of 10. The same experiment at pH 3 gave $Zn\cdot CR\cdot Br\cdot ClO_4$.

$Ni\cdot CR\cdot Cl\cdot ClO_4$ and *$Ni\cdot CR\cdot(ClO_4)_2$* were obtained as first and second crops of precipitate when excess $NaClO_4$ was added to the mother-liquor containing $Ni\cdot CR^{2+}$. The latter is the more soluble, and was obtained by chilling the solution.

Condensations involving zinc, cobalt or nickel salts and 3,2-triamine with DAP gave polymeric products which could not be purified; in the case of zinc there is IR evidence for the presence of a compound containing both imine and carbonyl groups, implying that the closure of the condensate ring has not occurred. With DFP, 3,2-triamine and zinc ions high yields of an off-white powder which analysed as $Zn_3Br_2(ClO_4)_4C_{30}H_{34}N_{10}(H_2O)_6$ were obtained. The analysis suggests a mixed oligomer, similar to those obtained by Lions.[7]

It was also found that under the conditions of method A isolable condensates could be formed between zinc or copper ions, DAP and ethylenediamine(en) when their molar ratio was 1:1:1, although these condensates could not be definitely characterised. When the ratio was 1:1:2 no products could be isolated. The rate of disappearance of DAP was followed and was found to be greater with a copper:en ratio of 1:1 than with a ratio of 1:2 (although amine stability constants preclude identical conditions of pH). The zinc case was complicated by the fact that the reaction did not appear to proceed to completion.

Results

Infrared Spectra

Some C=N stretching frequencies are presented in Table II; the assignments are discussed elsewhere.[8] The change in ring size does not have a marked effect on the position of this mode of vibration; the position of the C=N vibration of the pyridine ring is more variable than in complexes of mono-imino derivatives.[3]

The formulation as a ternary complex of the copper compound of DAP and the 3,2-triamine is supported by its IR spectrum. The strong C=O stretching vibration occurs at 1698 cm^{-1} and the C=N stretch of the

TABLE II. Infra-Red Data.[a]

Compound	C=N Stretch (cm^{-1})	C=N (Pyridine) (cm^{-1})
Ni·3,4-CR·2H_2O·2ClO_4	1628	1595
Cu·3,4-CR·H_2O·2ClO_4	1635	1588
Zn·3,4-CR·Br·ClO_4	1653, 1633	1595
Zn·CR·Br·ClO_4	1648	1588
Zn·*des*-diMeCR·Br·ClO_4	1653	1602
2,6-diacetylpyridine	(C=O) 1708	1580
2,6-diformylpyridine	(C=O) 1725	1587

[a] Nujol mulls on a Perkin–Elmer 257. Calibrated against polystyrene.

pyridine ring at 1596 cm^{-1}; there is no evidence of a C=N stretch due to a Schiff-base linkage. The N–H stretching modes of the primary amine occur at 3285 and 3335 cm^{-1} and that of the secondary amino group at 3180 cm^{-1}.

The region above 3100 cm^{-1} in the spectrum of $(Zn \cdot CR)_2OH \cdot H_2O(ClO_4)_3$ shows bands at 3255, 3197 and 3550 cm^{-1}, which we attribute to NH, OH^- and H_2O stretching modes.

Ultraviolet Spectra

No systematic study has been reported of solution spectra of CR complexes: our results for these compounds are compared with those for the 3,4-CR complexes in Table III.

The zinc ion has a profound effect on the π-orbitals of the di-iminopyridine, as shown by comparing the spectrum of $ZnCR^{2+}$ with that of a metal-free CR analogue – the condensate of DAP with two molecules of cyclohexylamine. In methanol this has peaks at 240 nm (ε 3800) and 280 nm (ε 3700).

Only the d–d transitions are tabulated for the Cu^{II} and Ni^{II} complexes. In contrast to the transitions in the aromatic region shown for the Zn^{II} complexes these are quite markedly affected by the change in size of the macrocycle. The nickel spectra suggest high-spin octahedral stereochemistry;[9,10] identical spectra were obtained in acetonitrile. The spectrum of $CoCR^{2+}$ in water was identical to that in methanol,[6] attributed by Long and Busch to five-coordinate cobalt.

Magnetic Properties

The complex Ni·CR·$(ClO_4)_2$ has been reported to be diamagnetic while Ni·CR·Cl_2·$^1/_2H_2O$ is paramagnetic.[1] This and the high-spin state of the $[Ni \cdot CR \cdot (H_2O)_2]^{2+}$ ion are consistent with the unpairing of the d_{z^2} electrons in an increasing axial ligand field. It is therefore of interest to find out whether these electrons can be unpaired by the increased ligand field when one perchlorate is replaced by chloride. The magnetic moments of Ni·CR·$(ClO_4)_2$ and Ni·CR·Cl·ClO_4 were determined at room temperature (23° C) by the Gouy method. After correction for ligand and inner-core diamagnetism using Pascal's constants,[11] and for the expected temperature-independent paramagnetism in Ni complexes (estimated as 250×10^{-6} cgs units[11]) both values were 0 ± 0.15 B.M. It is interesting that Ni·CR·Cl·ClO_4 should be diamagnetic. The implication is that the compound has a structure similar to that of Ni·CR·Br_2·H_2O which is also diamagnetic and which contains nickel coordinated in a approximately square pyrimidal configuration with an N_4 base and a Br apex.[12]

Discussion

The ready synthesis of CR complexes contrasts with the unsuccessful attempts to synthesize under identical conditions complexes of 2,3-CR. Molecular models show not only that the 2,3 macrocycle would have a smaller aperture than the 3,3 derivative for coordination of the metal ion (*cf.* Ref. 8), but also that the

TABLE III. Ultra-Violet Spectra.[a]

Metal	λ_{max} (nm) (ε) CR macrocycle	λ_{max} (nm) (ε) 3,4-CR macrocycle
Zn^{II}	235–245(1.4×10^4) doublet 250(9.9×10^3) shoulder 290–310(4.5×10^3) triplet	235–245(1.4×10^4) doublet 250(1.2×10^4) shoulder 310(4.8×10^3) broad
Cu^{II}	560(1.3×10^2)	610(1.1×10^2)
Ni^{II}	470, 725 ($\varepsilon < 20$)	360(2) 475(3) 779(14) 828(18)

[a] Recorded in aqueous solution on a Unicam SP800 spectrophotometer from 230–850 nm.

former macrocycle would experience a much greater ring strain even without the metal being present. This implies a minimum ring size for the formation of this kind of macrocycle by triamine–diketone condensation.

The 3,4-CR macrocycle will not be constrained in the manner of 2,3-CR. However the metal complexes of 3,4-CR described above contain a seven-membered ring, and the instability of this ring is presumably the reason for the lower yields and lesser stability of 3,4-CR complexes *vis-à-vis* those of CR itself. One would expect corresponding behaviour from 2,4-CR.

The template synthesis requires strong complexation of the metal by the triamine, as is illustrated by the preparation of the N-methyl-CR complex of zinc. In this preparation a precipitate of zinc hydroxide was only avoided by adding excess acid, which protonated the amine and totally inhibited the reaction, or by adding to the reaction mixture an excess of sodium bromide. The latter increased the solubility product of zinc hydroxide by the primary electrolyte effect and by inner-sphere association between Zn^{2+} and Br^-. The difference is apparently due to the (approximately tenfold) lower formation constant of complexes of 3,3′-diamino-N,N-di-n-propyl-methylamine as compared with 3,3′-diamino-di-n-propylamine,[13] caused by crowding at the central nitrogen atom, and the consequent inability of the former ligand to compete with the metal for hydroxide at the pH value of the reaction. In the case of Cu^{II}, which binds amines more strongly, similar conditions suffice for the preparation of CR and N-MeCR complexes.

The experimental conditions required suggest that the reaction between DAP and 3,3-triamine is a true template reaction; that is to say, it involves reaction between substrates both of which are coordinated to the metal ion concerned. This is demonstrated particularly by the failure of reactions in which the metal ion is present as a suspension of its hydroxide, so that it is not coordinated by the triamine. If the condensation were successful – even to the point of forming the first Schiff base linkage without closing the ring – then the metal hydroxide would redissolve as the reaction proceeded. It is also interesting to note the formation of isolable condensates of 1 mole DAP and 1 mole ethylenediamine(en) in the presence of zinc and copper ions and the failure of similar reactions when the DAP to en ratio is 1:2. A possible explanation is that in the presence of four ligating groups (2 × en) the metal ion cannot, for steric reasons, accommodate a DAP molecule as well, DAP being a much weaker ligand then en. In copper this will be more pronounced on account of the weakening of the axial bonds that is common with hexacoordinate copper.

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